Lung Cancer Detection with Digital Chest Tomosynthesis

Baseline Results from the Observational Study SOS

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Introduction: Observational studies consistently support strategies for early cancer diagnosis and treatment. Owing to its high prevalence, mortality rate, and easily identifiable at-risk population groups, lung cancer seems ideal for early detection programs. We present the baseline results of the SOS study, a single-arm observational study of digital chest tomosynthesis for lung cancer detection in an at-risk population.

Methods: Accrual of study participants started in December 2010 and ended in December 2011. Participants considered eligible were smokers or former smokers aged 45 to 75 years, with a smoking history of at least 20 pack-years, without malignancy in the 5 years before the start of the study. A tomosynthesis examination was performed at baseline and another the year after.

Results: Of the 1919 candidates assessed, 1843 (96%) were enrolled into the study: the mean age was 61 years (range, 48–73 years); 1419 (77%) were current smokers. The most prevalent comorbidities were hypertension, chronic obstructive pulmonary disease, and cardiovascular diseases. A total of 1843 tomosynthesis studies were obtained. Pulmonary abnormalities were detected in 268 subjects (14.5%). First-line basal computed tomography (CT) was subsequently carried out in 132 subjects (7.2%), 68 (4.9%) of which were referred for follow-up CT. Positron-emission tomography/CT was performed on 27 individuals (1.46%), and lung cancer was detected in 18 (0.98%) of them.

Conclusion: The detection rate of noncalcified lung nodules for tomosynthesis was comparable with rates reported for CT. A small subgroup underwent low-dosage CT and entered a follow-up program. Overall, lung cancer was detected in approximately 1% of cases. Digital chest tomosynthesis holds promise as a first-line lung cancer screening tool.

Key Words: Lung cancer screening, Digital chest tomosynthesis.

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Lung cancer is the leading cause of cancer-related deaths in the United States and most of the western and developing countries. Most lung cancers are detected when patients become symptomatic and have late-stage disease. However, recently, computed tomography (CT) screening for lung cancer has been reported to reduce lung cancer mortality.[1] In this regard, the National Lung Screening Trial (NLST)[1] showed a 20% reduction in lung cancer-specific deaths in those patients who had screening performed with chest CT. However, CT is associated with the disadvantages of high radiation dosage and cost. Digital chest tomosynthesis (DT), a tomographic technique, may offer an alternative to CT screening. DT uses a conventional radiograph tube, a flat-panel detector, a computer-controlled tube mover, and special reconstruction algorithms to produce section images. Compared with conventional chest radiography, chest tomosynthesis improved sensitivity in the detection of CT-proven lung nodules. DT is able to detect most lung nodules larger than 5 mm, in particular 91% of nodules, whose sizes were between 4 mm and 6 mm, and 100% of nodules larger than 6 mm, detected in a CT scan.[2,3] In addition, the effective radiation dosage to patients from chest examination with DT is low (approximately 0.13 mSv compared with 0.1 mSv for a postero-anterior and lateral chest radiograph).[4] Although it lacks the depth resolution of CT, tomosynthesis provides some of the benefits of CT at lower costs and radiation dosages. Furthermore, DT is less expensive than CT at approximately one-sixths of the cost of a CT.[5]

In this single-arm observational study (SOS Study), DT was used for early detection of lung cancer. The study was approved by the Institutional Ethics Committee (approval no. 68/09). We report the results of the 1-year baseline DT in a population at risk of having lung cancer.

MATERIALS AND METHODS

Study Design

A sample size of 2000 subjects was planned, which was calculated on the basis of incidence and mortality data extracted from the Piedmont Cancer Registry.[6] Subject recruitment was through general practitioners, advertising leaflets, and the local media. Inclusion criteria were: current or former smoker status; smoking history of at least 20 pack-years; age

45 to 75 years; no history of cancer in the 5 years before the start of the study; and no chest CT study in the 12 months up to enrolment. For former smokers, the maximum time since quitting smoking was 10 years. Candidates were assessed for eligibility by telephone interview with the project assistant (Fig. 1). Written informed consent was obtained before entry into the study, in accordance with the requirements of the institutional review board and local health authorities, and a questionnaire was administered, investigating occupational history, smoking habits, and past and present health conditions. An additional inclusion criterion specific for image acquisition was that subjects be able to stand and hold their breath for 11 seconds.

Digital Chest Tomosynthesis

Under the study protocol, a tomosynthesis examination was performed at baseline in all subjects and another a year later in those with a negative baseline scan. In all, one baseline and a first-round examination were planned. All subjects were informed about their examination results by letter. Scans were obtained on a commercially available system (Volume RAD; GE Healthcare, Chalfont St Giles, England) consisting of an radiograph tube, a wall stand, a stationary antiscattered grid (70 lines per cm; ratio 13:1), and a cesium iodide amorphous silicon (Csl/a-Si) flat-panel detector system ($41 \times 41\,cm^2$; $200 \times 200\,mm^2$ pixel size). A mean of 60 projection images were acquired along a vertical path of 60° of total tube angular motion (Fig. 2). A

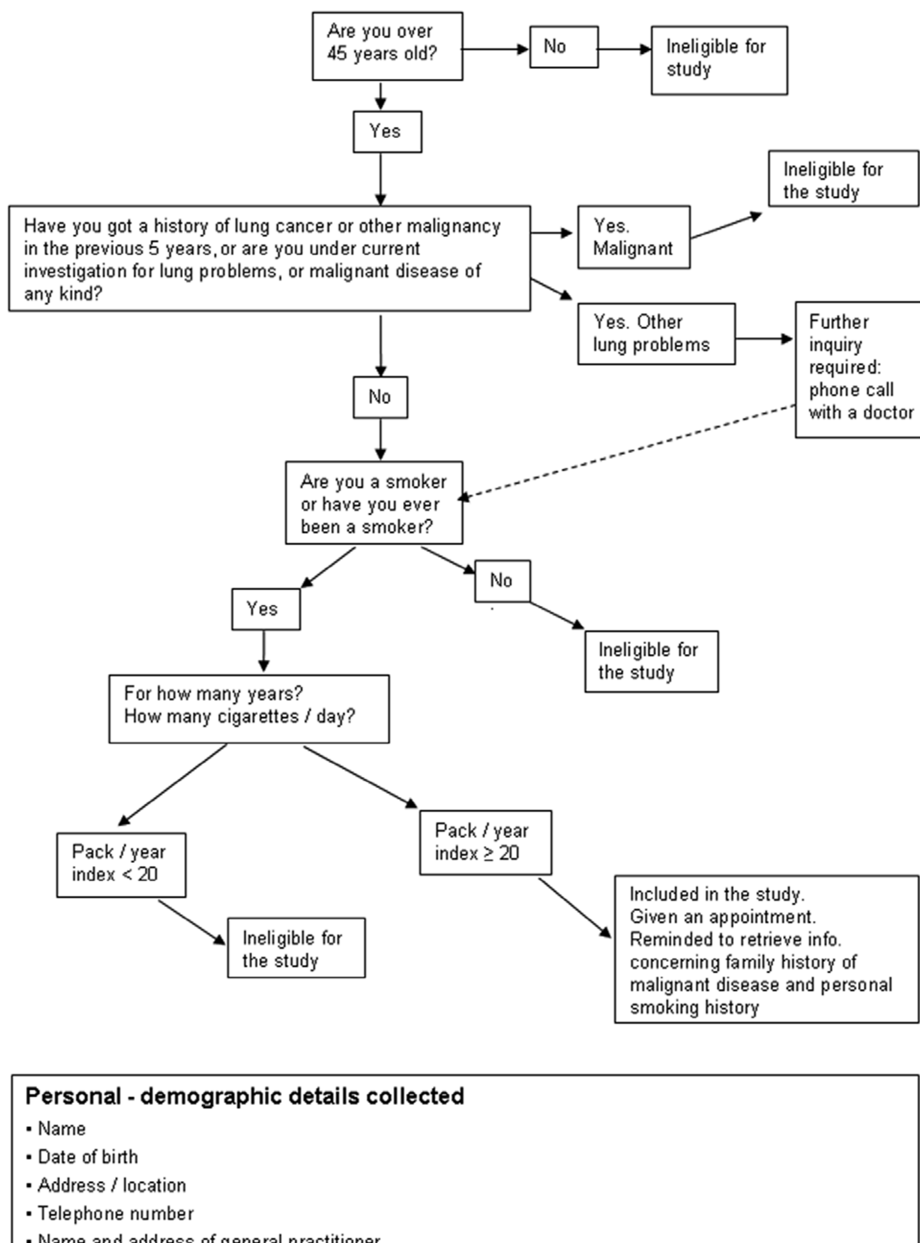

FIGURE 1. Telephone questionnaire—eligibility criteria.

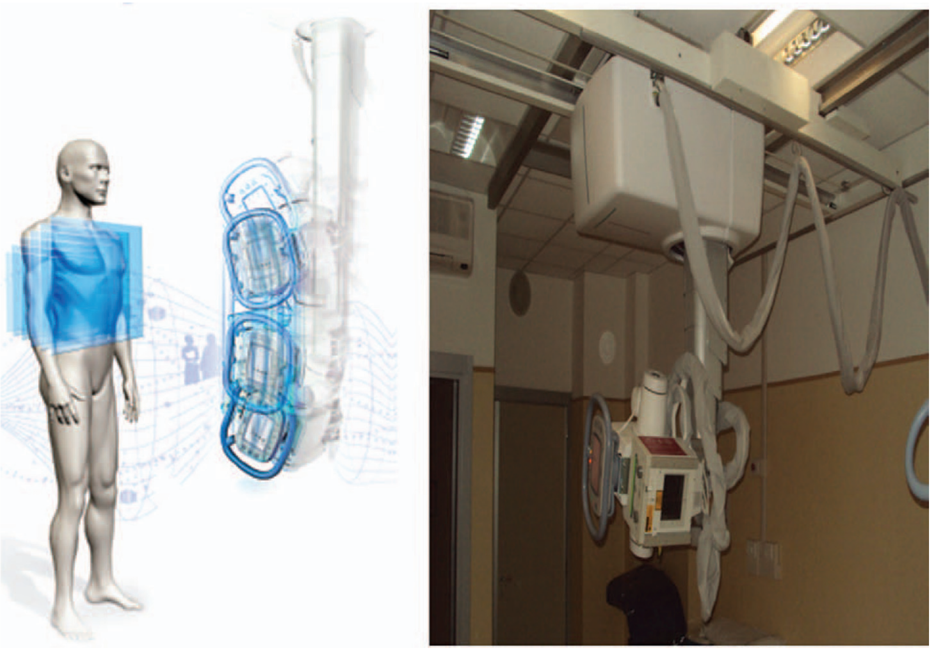

FIGURE 2. Digital chest tomosynthesis.

set of images were acquired in 10 to 12 seconds of breath-hold condition, which these asymptomatic subjects easily achieved. The images were then reconstructed in 3-mm plane spacing in the coronal plane. Image reconstruction was done using the matrix inversion tomosynthesis algorithm (simultaneous algebraic reconstruction technique), and a sliding average of seven adjacent planes was selected to reduce noise and low-contrast tomosynthesis artifacts. The mAs in roentgenogram were set with an automated control of the exposure to be 10 times lower than the ones used for the chest radiograph. A scout image (chest radiograph) was obtained to check patient position; if satisfactory, the system then calculated the appropriate low-dosage exposure (mAs) for the tomosynthesis scan. The acquisition data are reported in Table 1. The images fully covered the field from the anterior skin to the back of the chest.

Interpretation of Tomosynthesis Images

Two radiologists independently viewed the tomosynthesis images. One had more than 20 years of experience with chest imaging and 1 year of clinical experience with tomosynthesis. The other has 5 years of experience with chest imaging and a few months of clinical experience with tomosynthesis. Both observers were instructed to mark the lung nodules on the tomosynthesis images. Each nodule was marked on only one image per imaging technique and in the most prominent location. The observers were allowed to change window width and level and image contrast, and use the pan and zoom functions. All readings were performed on a picture archiving and communications system-integrated workstation. The largest diameter in the transverse plane was measured. Lung nodules or opacities were classified as definitely benign (completely calcified or with a calcification pattern typical of benign disease) or uncertain (possible lung cancer nodule).

Interpretation and Workup of Suspicious Pulmonary Abnormalities

For subjects with a benign nodule or a nodule 5 mm or less in size, a second tomosynthesis study was performed a year later. Subjects, with an uncertain nodule larger than 5 mm or with multiple nodules were defined as positive and underwent low-dosage CT or contrast-enhanced CT, depending on the nodule size, and in keeping with the Fleischner Society guidelines for the management of small pulmonary nodules.[7] Diagnostic CT was performed on a

TABLE 1. Acquisition Parameters of Digital Chest Tomosynthesis and Chest CT Images

Images and Parameters	
Digital chest tomosynthesis	
Voltage	120 kV
Detector entrance dosage	0.5 µGy
Nominal focal spot	0.6 mm
Additional copper filtration	0.1 mm
AEC speed	400
Average	300 mAs
Dosage ratio	1:10
Total exposition time	11.4
Mean number of images	94
Rotation angle	30°
Gap	3 mm
Chest CT	
Voltage	120 kV
Total exposition time	0.4
Average	250 mAs
Pitch	1.5

CT, computed tomography; AEC, automatic exposure control.

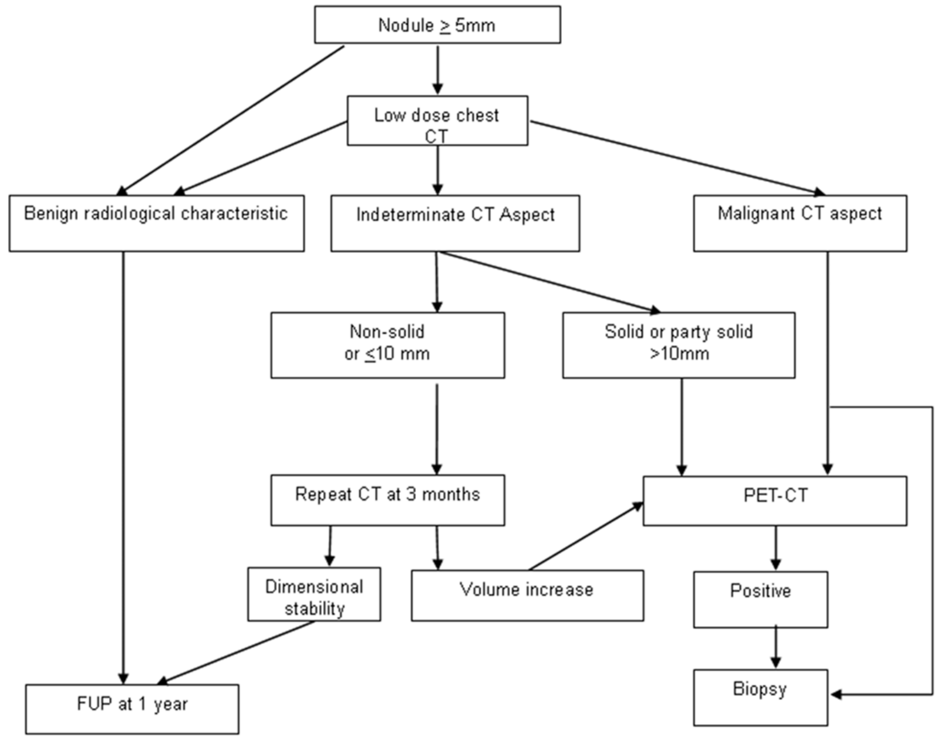

FIGURE 3. Early detection with tomosynthesis: patient management protocol. CT, computed tomography; PET-CT, positron-emission tomography computed tomography; FVP, .

Brilliance 64 scanner (Philips, Eindhoven, The Netherlands). A helicoidal CT scan was acquired, with 120 kV, 300 mAs, rotation time 0.42 seconds, pitch 1.5, and 5-mm slice thickness. CT was performed in accordance with the Fleischner Society guidelines.[7] If the CT scan confirmed a nodule less than 10 mm and showed nonsuspicious characteristics, it was defined as possibly benign, and the subject was asked to return for follow-up CT at 3 or 6 months, and then again at 12 months. If the CT scan confirmed a nodule larger than 8 mm with not definitely benign features, invasive diagnostic testing was considered and positron-emission tomography (PET) was performed. If the PET scan was positive, tissue diagnosis was obtained by bronchoscopy, percutaneous fine-needle aspiration biopsy, or video-assisted thoracoscopic surgery or thoracotomy. If the PET scan was negative, close follow-up was preferentially chosen and biopsy recommended, if the nodule had meanwhile grown in size (Fig. 3). Subjects noted to have mediastinal enlargement, pleural effusion or tumor, or lytic bone lesions were referred for further diagnostic testing (CT, thoracoscopy, bronchoscopy, or biopsy according to internal hospital guidelines). All uncertain cases were reviewed by an interdisciplinary team, including the radiologist, thoracic surgeon, and pneumologist. The primary endpoints were, detection rate of lung nodules by tomosynthesis compared with postero-anterior chest radiography (the scout image), the prevalence of lung cancer in this at-risk population, and tumor stage distribution.

Statistical Analysis

Raw data and proportions were compared using the χ^2 test or Fisher's exact test; mean values were compared with the *t* test using Satterthwaite approximation in case of heteroskedasticity. McNemar's test was applied to assess improved observer performance in correctly diagnosing pulmonary nodules. The weighted *k* statistic was calculated to assess interobserver agreement. Significant differences were defined as *p* values less than 0.05. Statistical analysis was carried out using Mathematica 8.0 (Wolfram Research).

RESULTS

Accrual started in December 2010 and closed in January 2011. A total of 1919 candidates underwent baseline clinical assessment and 76 of them were considered ineligible. The two most common reasons for noneligibility were, history of cancer and insufficient exposure to cigarette smoking. The mean age was 61 years (95% confidence interval, 48–73); on average, they smoked 580 cigarettes yearly during their life (95% confidence interval, 420–1400); 29% of the subjects were smokers at the time of accrual. Comorbidities are listed in Table 2.

TABLE 2. Comorbidities

Comorbidities	No. (%)
Asbestosis	2 (0.1)
Chronic obstructive pulmonary disease	242 (12.7)
Tuberculosis	31 (1.6)
Pleuritis	70 (3.7)
Previous pneumothorax	35 (1.8)
Asthma	89 (4.7)
Cardiopathy	201 (10.5)
Goiter	183 (9.6)
Previous neoplasm	117 (6.1)

TABLE 3. Number of Lung Nodules Detected with Tomosynthesis, Chest Radiography and Chest CT

Lung Nodules	Digital Tomosynthesis – No. (%)	Chest Radiography – No. (%)	Chest CT – No. (%)
5–8 mm	53 (91.4)	11 (19.0)	58 (100)
8–10 mm	40 (97.6)	15 (36.6)	41 (100)
>10 mm	33 (100)	21 (63.6)	33 (100)
Total	126 (95.45)	47 (35.6)	132 (100)

Values in parentheses are the difference in percentage as compared against chest CT; a significant difference emerged between the detection rate for tomosynthesis versus chest radiography ($p = 0.0306$) but not for tomosynthesis versus low-dosage CT ($p = 0.9521$). Statistical significance was set at $p < 0.05$.
CT, computed tomography.

Overall, 268 subjects (14.8%) had abnormlal findings at the baseline tomosynthesis examination. The number of nodules found in each patient varied from 1 to 12. The detection rate with tomosynthesis for all nodules was 18.4%; 7.2% of pulmonary nodules were indeterminate and larger than 5 mm. Low-dosage CT was subsequently performed in 132 subjects (7.2%): 39 were false-positives (extrathoracic nodules, pleural plaques) and 93 had one or more than one lung nodules larger than 5 mm in size. A comparison between the tomosynthesis and CT scans showed that the average difference in nodule diameter was 0.085 ± 1.820 mm. The nodules were grouped by diameter into three classes (Table 3). Among the subjects who underwent low-dosage CT after tomosynthesis, the nodule detection rate with tomosynthesis was statistically significant ($p = 0.0306$), and higher than with the scout chest radiograph for all three nodule groups, and total number of nodules detected; however, there was no statistically significant difference ($p = 0.9521$) between the nodule detection rate with tomosynthesis compared with CT. A PET/CT study was obtained in 27 (1.5%) and a follow-up CT done on 68 subjects (3.7%), respectively.

Video-assisted thoracoscopic surgery for indeterminate pulmonary nodules other than lung cancer was performed in six subjects (tuberculosis nodule [*n* = 1], mucosa-associated lymphoid tissue nodule [*n* = 1], hamartochondroma [*n* = 3], and an intrapulmonary lymph node [*n* = 1] which had increased in size at follow-up CT) and no complications developed.

Tomosynthesis examination led to the discovery of: extrapulmonary tumor (lymphoma [*n* = 1]); interstitial lung disease (*n* = 2); severe upper-lobe bullous emphysema (Fig. 4); and nonpulmonary pathological findings in 13 other patients (pleural effusion [*n* = 4]; pleural lesions [*n* = 5]; mediastinal enlargement [*n* = 4]). There were no interobserver differences regarding the sensitivity to detect benign lesions ($p > 0.15$ for benign nodules; McNemar test). One patient with abnormal findings on baseline CT and CT/PET refused further diagnostic testing.

Overall, the lung cancer prevalence was 97.67 out of 10,000 (18/1843). Table 4 reports tumor stage and histology. Adenocarcinoma was the most frequent histological type: clinical stage IA in six cases (Figs. 5 and 6); IB in two; IIA in two; IIB in one; IIIA and IIIB in one case each; and IV in five. Surgery for lung cancer was performed in 12 of 18 subjects (66.6%) (lobectomy [*n* = 11] and pneumonectomy [*n* = 1]); six subjects received chemotherapy and/or radiotherapy for inoperable disease.

DISCUSSION

After the release of the NLST results, regular annual low-dosage CT has been strongly recommended for the target

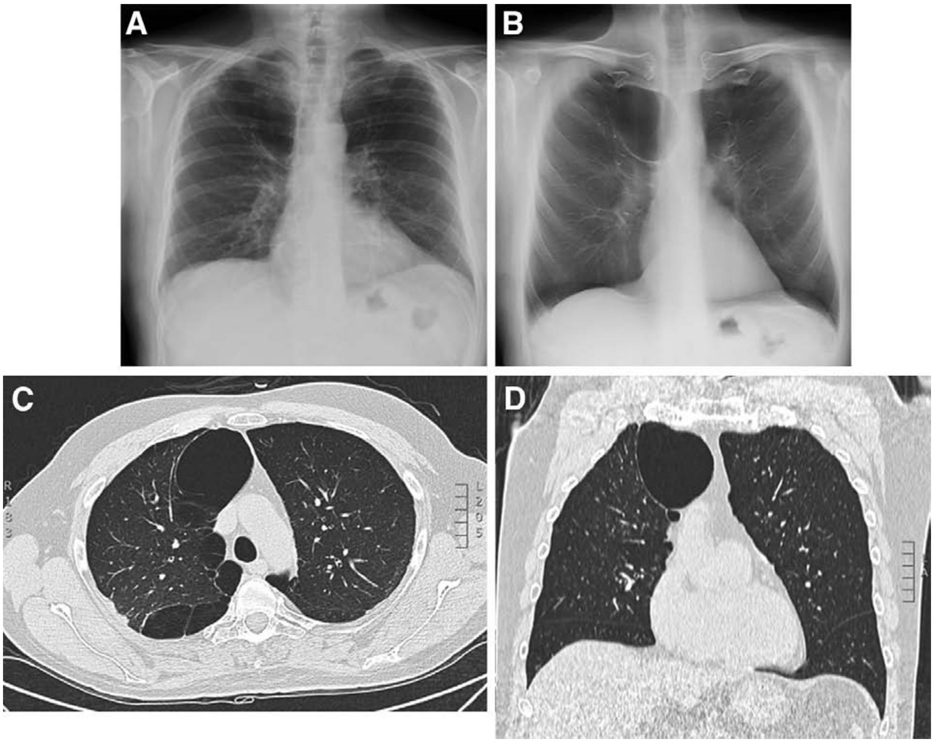

FIGURE 4. Digital chest tomosynthesis image (*B*) showing severe lung emphysema in a smoker, which was barely visible on the chest radiograph (*A*). *C,* Chest computed tomography scan confirmed the tomosynthesis findings (*D*).

TABLE 4. Tumor Stage and Histology in Subjects with Lung Cancer Diagnosed by Tomosynthesis

Tumor stage	No. of subjects
IA	6
IB	2
IIA	2
IIB	1
IIIA	1
IIIB	1
IV	5
Histology	No. of subjects
Adenocarcinoma	10
Squamous cell carcinoma	7
Carcinoid	1

group of heavy smokers (30 pack-years; 55–74 years of age) by the American Association for Thoracic Surgery.[8] General public opinion widely supports cancer screening: 87% of interviewees believed that it is almost always a good idea; 75% were sure that it saved lives most or all the time; a substantial proportion believed that an 80-year-old person choosing not to be screened was irresponsible.[9] Nonetheless, the adsorbed radiation dosages and costs associated with low-dosage CT screening encourage the search for other strategies for the early detection of lung cancer, or to select among individuals at high risk, those who should be referred for low-dosage CT.

The risk of developing a new cancer because of radiation exposure should not be underestimated. Chest CT screening can be accomplished at an average effective dosage of 2 mSv, and the mean effective dosage in the NLST was 1.4 ± 0.5 mSv. But low-dosage CT must be repeated over a period of several years and twice a year in some cases. The estimated radiation dosage that each NLST participant received was approximately 8 mSv.[10] The estimated annual average effective dosage equivalent that people receive from natural sources is more than 3 mSv.[11] Moreover, flight passengers are exposed to radiation during supersonic flight. During a 10-hour flight at 60,000 to 70,000 feet, for example, a passenger receives a dosage equivalent as high as 0.27 mSv, with frequent flyers easily accumulating multiple radiation dosages.[12]

By contrast, the natural radiation dosage in a low-dosage CT screening program exposes a person to approximately 20

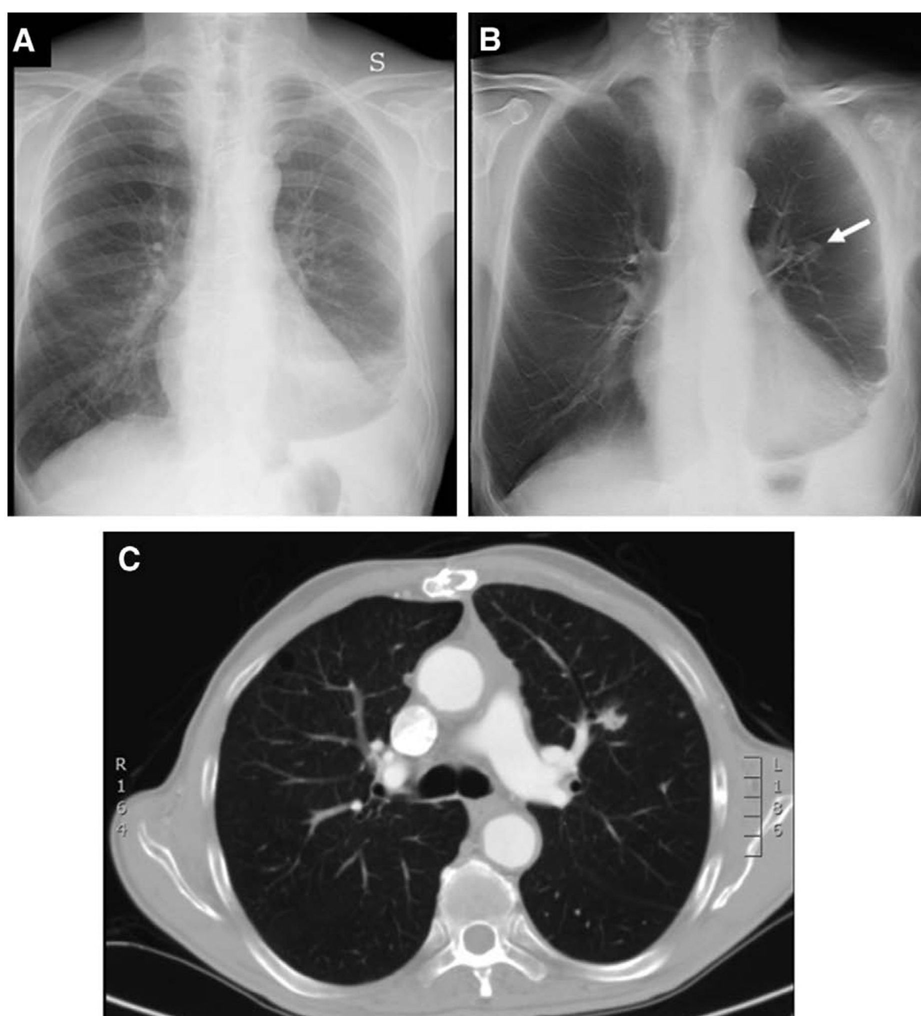

FIGURE 5. Digital chest tomosynthesis image showing a solid pulmonary nodule in a 63-year-old man. *A,* The pulmonary nodule is not visible on the postero-anterior chest radiograph. *B,* tomosynthesis planes showing solid nodular opacity (white arrow) in the left upper lung, with peripheral spiculations that revealed a pulmonary location. *C,* computed tomography image (lung window, transverse plane) confirming the nodule, with a similar extension as shown by tomosynthesis.

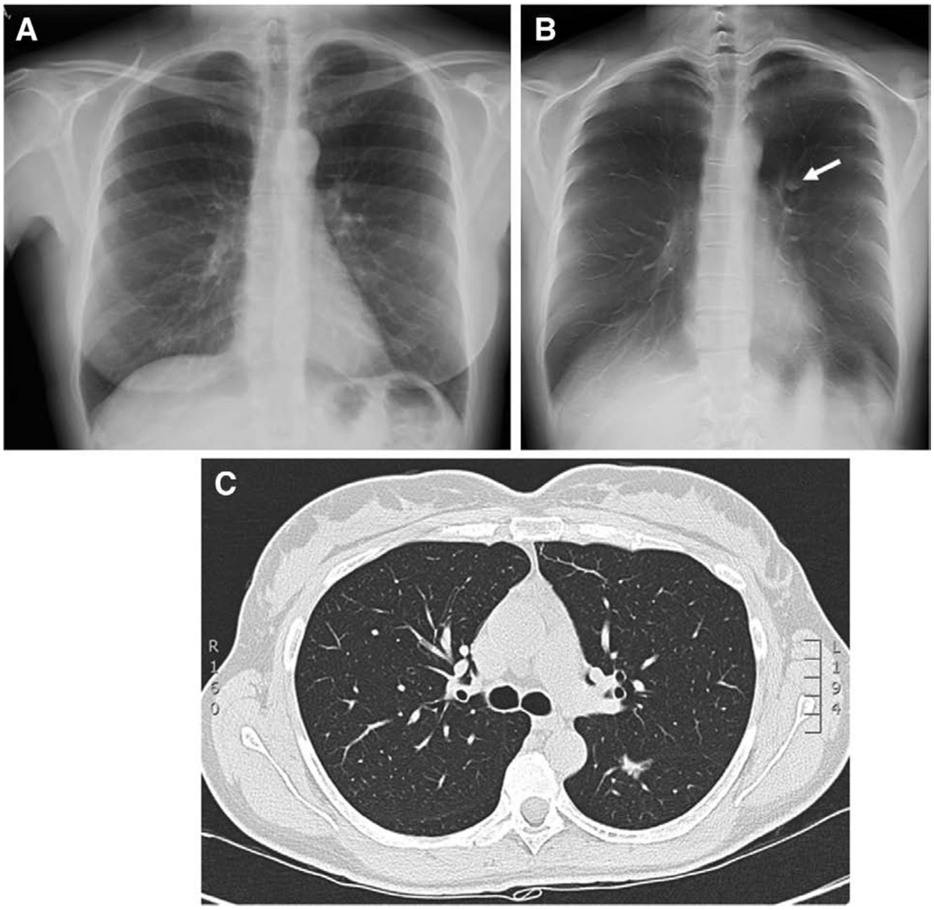

FIGURE 6. Digital chest tomosynthesis image showing a solid pulmonary nodule in a 47-year-old woman. *A,* The pulmonary nodule is not visible on the postero-anterior chest radiograph. *B*, tomosynthesis planes showing solid nodular opacity (white arrow) in the left lower lung, with peripheral spiculations that revealed a pulmonary location. *C,* computed tomography image (lung window, transverse plane) confirming the nodule in the left lower lobe.

mSv, if other radionuclide investigations are performed in the meanwhile (e.g., nuclear cardiac imaging, PET/CT), or the person is not a frequent flyer. The cumulative radiation dosage can thus, rise to levels that pose an individual at risk of developing a second malignancy. According to the NLST report, data models predict that approximately one cancer death may be caused by radiation from imaging, per 2500 persons screened. The cancer incidence (International Commission on Radiation Protection publication recommendations stochastic risk coefficient) is one of 3710 for a single low-dosage CT study, whereas the mean effective dosage for tomosynthesis is approximately 0.13 mSv (International Commission on Radiation Protection stochastic risk coefficient 1 of 75,757).

The NLST, the most expensive randomized trial of a single cancer-screening test ever undertaken in the history of U.S. medicine, cost $200 million.[1] The cost for a low-dosage CT examination in lung cancer screening is approximately $300, whereas a mammogram costs from 80 to $150. Critics of lung cancer screening with low-dosage CT have pointed to the limitations inherent to health cost analyses based on simulation modeling.[13] Clarification expected from the NLST cost-effectiveness evaluation may help to settle some of the controversy surrounding low-dosage CT screening. Added to these concerns are the impact of lung cancer screening on medical resource allocation (cost of low-dosage CT screening and additional testing). For each low-dosage CT screen for lung cancer, Medicare (the United States health insurance program for the elderly and disabled) reimburses approximately $300. With the number of high-risk individuals eligible for lung cancer screening currently at nearly seven million (based on NLST data), the annual cost in the United States alone would total approximately $2.1 billion.

Limiting screening to high-risk patients could eliminate unnecessary procedures in individuals with a lower risk of cancer and keep a screening program more cost-effective. For example, prescreening based on age, smoking history, personal and family medical history, and occupational history would be one way to identify high-risk population subsets. Other factors, including the screening interval, will come into the cost calculation. Because low-dosage CT imaging is more expensive than many other screening modalities, validating its effectiveness is certainly warranted. As a potential alternative, DT has been shown to be superior to chest radiography in the detection of pulmonary nodules[14,15]: it detected 91% of nodules between 4 mm and 6 mm, and 100% of nodules larger than 6 mm found by CT. Recently,[16] tomosynthesis was compared versus CT in its ability to detect artificial pulmonary nodules 5 and 8 mm in diameter and ground glass opacities in a phantom. The detectability indices for tomosynthesis and CT were similar.

In our observational study involving nearly 2000 subjects, the percentage of lung nodules and lung cancer detected with tomosynthesis was comparable to that reported for low-dosage CT. The lung cancer detection rate was 0.9% (early stage disease in 10 of 18 subjects [55%] and inoperable stage IV disease in five of 18 subjects [27%]). By restricting the age range to 55 to 79 years, and raising the number of pack-years to 30, as in the NLST, an even higher incidence of lung cancer might have been detected. Admittedly, many of the health risks of screening will remain also with a wider use of tomosynthesis for cancer screening, as the NLST reported. Such risks will need to be balanced against the greater reduction in radiation exposure and screening costs.

CONCLUSION

The baseline results on the use of DT in the early detection of lung cancer are encouraging; the detection rate is comparable to the rates reported for low-dosage CT and is attained at a far lower cost and radiation dosage. The first-round tomosynthesis screen will provide further data about its effectiveness in the follow-up of high-risk subjects. Experimental studies support the use of tomosynthesis to select those suitable for CT among high-risk people. Studies on a larger number of subjects are needed to confirm these results.

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